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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/535,433	02/02/2006	Lorenzo Frigerio	1009-0118PUS1	8447
2292 7590 09/11/2008 BIRCH STEWART KOLASCH & BIRCH PO BOX 747 FALLS CHURCH, VA 22040-0747			EXAMINER BRISTOL, LYNN ANNE	
			ART UNIT	PAPER NUMBER
			1643	
			NOTIFICATION DATE	DELIVERY MODE
			09/11/2008	ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

<p align="center"><b>Advisory Action</b> <b>Before the Filing of an Appeal Brief</b></p>	<p><b>Application No.</b> 10/535,433</p>	<p><b>Applicant(s)</b> FRIGERIO ET AL.</p>	
	<p><b>Examiner</b> LYNN BRISTOL</p>	<p><b>Art Unit</b> 1643</p>	

**--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

THE REPLY FILED 21 August 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
- b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
- Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on 7/25/08. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

#### AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
- (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
- (b) ☐ They raise the issue of new matter (see NOTE below);
- (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
- (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: \_\_\_\_\_. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): 112, 2<sup>nd</sup> paragraph rejections.
6. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
- The status of the claim(s) is (or will be) as follows:
- Claim(s) allowed: \_\_\_\_\_.
- Claim(s) objected to: 39.
- Claim(s) rejected: 1,34-38, 40-44,46,48,50,52 and 82-87.
- Claim(s) withdrawn from consideration: 45,47,49,51 and 53-81.

#### AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

#### REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:  
See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). \_\_\_\_\_
13. ☐ Other: \_\_\_\_\_.

/David J Blanchard/  
Primary Examiner, Art Unit 1643

Continuation of 11. does NOT place the application in condition for allowance because:

112, 1st paragraph (written description) is maintained for Claims 1, 34-38, 40-44, 46, 48, 50, 52 and 82-87. Applicants allege the claims are directed to a method of making antibodies. Applicants allege the rejection is misplaced because the written description for following the method steps is taught in the specification and that in practicing those steps, the specification need not demonstrate that a reasonable number of working embodiments for modified antibodies are actually obtained.

#### Response to Arguments

The schematic provided in the response on p. 16 outlining the method steps fails to include the final step of screening for functional antibodies, where a functional antibody is required to meet the following criteria a) retains antigen binding, b) the vacuolar targeting signal encoded within the immunoglobulin heavy chain is removed or reduced in its effectiveness, and c) antibody secretion is improved. The data from Figures 6, 7, 9 and 10 shows that examples of C-terminal modified antibodies produced by the method were in fact further examined or screened to see whether antibody secretion was improved (i.e., the transport of the antibody to vacuole was reduced or eliminated). Further, the claim language in Claim 1, element (b) requires that the vacuolar targeting is removed or reduced, and thus absent further screening steps for working embodiments, it is not clear how the ordinary artisan could generate the genus of functional antibodies in view of the broad number of possible modifications introduced into the antibody format in following the method steps.

112, 1st paragraph (enablement) is maintained for Claims 1, 34-38, 40-44, 46, 48, 50, 52 and 82-87. Applicants allege the same rejection was made in *Ex parte Kubin*. Applicants excerpt *Kubin* for the aspect of the decision stating "the amount of experimentation to practice the full scope of the claimed invention might have been extensive, but it would have been routine. The techniques necessary to do so were well known to those skilled in the art." *Id* at 1416. Further, the Hunter et al. publication confirm that vacuole sorting signal sequences work across species.

#### Response to Arguments

The examiner respectively submits that the facts and the claim scope in *Kubin* are unlike the instant case. The claims adjudicated in *Kubin* were directed to polynucleotides encoding polypeptides "at least 80% identical to amino acids 22-221 of SEQ ID NO:2' binding to "CD48." Here instant claim 1 is broader in scope than the claims in *Kubin*, because in *Kubin*, the extent of variation could be no more than 20% (or at least 80% identical). Here, there is no limitation as to what constitutes "the modifying" in the region of "the nucleotide sequence encoding the C-terminus 18 amino acids of the immunoglobulin heavy chain molecule." Further, there is no claimed requirement that the final product binds to any antigen. As stated in the Office Action of 1/25/08, the scope of the "modification" encompasses a) one or more point mutations; b) one or more nucleic acid deletions; c) one or more nucleic acid additions, and/or d) one or more nucleotides replaced with a synthetic nucleotide sequence.

103(a) rejection is maintained for Claims 1, 34, 35, 40, 41, 46, 48 and 50. Applicants allege element (b) of Claim 1 is not taught in the cited art references.

#### Response to Arguments

None the individual references taken alone teach the exact language in element (b) of Claim 1 but the claims are not patentably distinguishable in view of the combined disclosures because of the reasons set forth in the Office Action of 6/21/07, and further when considered under the recent KSR decision. Under the recent KSR decision, the cited references of art are not required to "explicitly teach or suggest" all of the steps or elements. The Supreme Court has determined in *KSR International Co. v. Teleflex, Inc.*, 550 U.S. \_\_, 82, USPQ2d 1385 (2007), that "a person of ordinary skill attempting to solve a problem will" not "be led only to those elements of prior art designed to solve the same problem....." (KSR, 550 U.S. at \_\_, 82 USPQ2d at 1397). In addition, the court found that "When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variant, 35 USC 103 likely bars its patentability" (KSR, 550 U.S. at \_\_, 82 USPQ2d at 1396). Further the court found that the Federal Circuit has erred in applying the teaching-suggestion-motivation test in an overly rigid and formalistic way, in particular by concluding "that a patent claim cannot be proved obvious merely by showing that the combination of elements was 'obvious to try'" (KSR, 550 U.S. at \_\_, 82 USPQ2d at 1397) and has further determined that ".....[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results" (KSR, 550 U.S. at \_\_, 82 USPQ2d at 1395). The court further found that "..... the conclusion that when a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious" (KSR, 550 U.S. at \_\_, 82 USPQ2d at 1395-1396). Thus, when considering obviousness of a combination of known elements, the operative question is "whether the improvement is more than the predictable use of prior art elements according to their established functions" ((KSR, 550 U.S. at \_\_, 82 USPQ2d at 1396).